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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,440	01/19/2000	DAVID PHILIP LANE	39749-0001APC	7276

25213 7590 12/13/2006

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/403,440	**Applicant(s)** LANE, DAVID PHILIP	
	Examiner MINH-TAM DAVIS	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 September 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *none*.
   Claim(s) objected to: *none*.
   Claim(s) rejected: *1,2 and 8*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-2, 8 are examined in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bottger et al, 1996 (Oncogene, 13: 2141-2147), in view of McCann A H et al, 1995 (British J Cancer, 71(5): 981-5), and further in view of Lee JM et al, 1995 (Cancer and metastasis Review, 14(2): 149-161) for reasons already of record in paper of 07/18/06.

A. The response asserts that the specification discloses that "cells that do not overexpress mdm2" includes all cells in which mdm2 is present at low or normal level. The response cites the studies by Buesco-Ramos et al, 1993, and Sheikh et al, 1993, as referred by McCann et al, in which the increased level in mdm2 mRNA is found in patients with no alteration in mdm2 copy number. The response concludes from these studies that where there is no amplification of the gene, the protein may still be overexpressed. The response asserts that that the Examiner is wrong to say that McCann et al teach that "in cancers which do not express

mdm2 such as breast cancer cells, the protein expression of mdm2 is significantly associated with low level of p53". The response asserts that the MDM2+ status is associated with overexpression of mdm2 (i.e. 7% of the samples, having 10-50% nuclear staining). The response asserts that McCann et al teach that MDM2+ is significantly associated with low levels of p53.

The response of 09/18/06 has been considered but is not found to be persuasive for the following reasons:

Contrary to the response assertion, there is **no evidence** that McCann et al teach that **mdm2+ status** (type 2) indicates **overexpression** of mdm2. From the teaching of McCann et al, one would understand that for mdm2+ or mdm2 type 2, only 10 to 50% of cells are detected with mdm2 protein, and for mdm2 type 1, even less mdm2 protein is detected, i.e. less than 10% of cells are detected with mdm2 protein (Table 1 on page 983). Of note is that type 3, where more than 50% of cells are detected with mdm2 protein, **does not even exist** in breast cancer (table 1, second column). It is not clear based on what facts that Applicant interprets as overexpression, when only 10 to 50% of cells are detected with mdm2 protein.

Further, from the data taught by McCann et al, it is clear that in **table III**, on page 983, the presence of mdm2 protein is **correlated** with low level of p53, even for breast cancer type 1 in which only less than 10% of cells express mdm2 protein. For example, with mdm2 type 1 and type 2, where the **mdm2** protein is expressed **even at less than 10 %** or between 10-50% of cells, respectively, as much as 12 of the total 14 (column 4 under Type 1) or 6 of the total 7 (column 3 under Type 2) patients have type 1 or negative p53; whereas in the absence of detectable mdm2 protein, only 40 of the total 74 patients have type 1 or negative p53, and 34 from the total of 74 patients have type 2 or 3 p53 (see also p.983, first column, last nine lines). It

is noted that in type 1 p53, less than 10% of cells express p53. Thus from the teaching of McCann et al, one would conclude that in breast cancer cells, the presence of mdm2, even at less than 10% of cancer cells, or between 10-50% of cancer cells, is significantly associated with low level of p53.

Further, from the teaching of McCann et al, it is clear that there is no correlation between mdm2 gene copy number and level of mdm2 protein, because **negative mdm2 staining** is also found in sample having mdm2 amplified, and because the same type 2 mdm2 is found in samples having both mdm2 amplified and non-mdm2 amplified (table II on page 983). Thus in view of the teaching of McCann et al, one cannot predict that increased mdm2 protein level is found in mdm2 type 2 breast cancer having no alteration of mdm2 copy number, nor one can extrapolate from the increased level in mdm2 **mRNA** in patients with no alteration in mdm2 copy number in the studies by Buesco-Ramos et al, 1993, and Sheikh et al, 1993, to the increase in the **protein** level of mdm2 in breast cancer patients with no alteration in mdm2 copy number, because the level of mRNA expression cannot be predictably correlated with the protein level of the encoded protein.

B. The response asserts that from reading Bottger et al one would believe that therapeutic targeting of mdm2/p53 interaction is of use specifically in cells where mdm2 is over-expressed. The response asserts that there is nothing in McCann to contradict this or to suggest that targeting of the mdm2/p53 may also be of use when mdm2 is not over-expressed.

The response of 09/18/06 has been considered but is not found to be persuasive for the following reasons:

The cited references clearly provide motivation for using a peptide inhibitor of mdm2 and p53 interaction, for treating those cancer cells that do not overexpress mdm2, because in these cancer cells, the level of p53 is low, and is associated with the expression of mdm2, as taught by McCann et al.

That is, it would have been obvious to use the peptide comprising the 12 amino acid peptide M**P**RFM**DY**WEGLN taught by Bottger et al to target cancer cells that express p53 and mdm2 to increase p53 function, including those populations of cancer cells that do not overexpress mdm2, such as in breast cancer cells, taught by McCann et al, because of the following reasons:

1) Loss of p53 function is correlated with increased resistance to chemotherapeutic agents, as taught by Lee et al,

2) hdm2 binding to the tumor suppressor protein p53 has been known to inactivate p53 function, and it is desirable to design synthetic peptides that interfere with the mdm2-p53 interaction and restore p53 function in human tumors that as taught by Bottger et al, and

3) In cancers which do not overexpress mdm2, such as breast cancer cells, the presence of mdm2 is significantly associated with low level of p53, as taught by McCann et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
November 27, 2006

SHANON A. FOLEY
SUPERVISORY PATENT EXAMINER